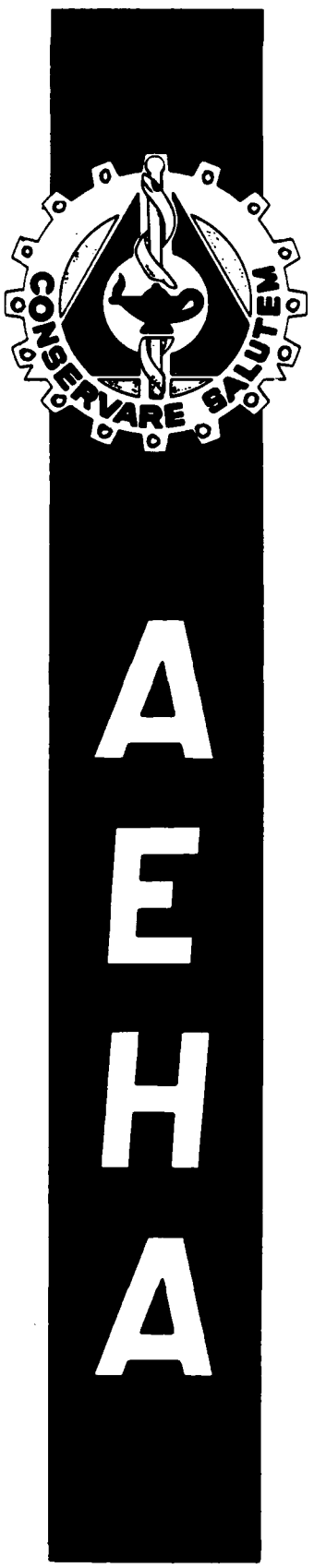

UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

PHASE 4
TOXICOLOGICAL STUDY NO. 75-51-0497-91
ASSESSMENT OF THE DEVELOPMENTAL TOXICITY
OF ZINC NAPHTHENATE IN RATS
JUNE 1985 - JULY 1988

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Under the command jurisdiction of the U.S. Army Health Services Command, AEHA's mission is to support the worldwide preventive medicine programs of the Army and other Department of Defense and Federal agencies.

The Agency is unique with the variety of scientific disciplines working together in one military unit to protect the health and well being of soldiers and civilians and enhance the environment.

This is accomplished through support in environmental quality, occupational and environmental health, toxicology, industrial hygiene, radiation and entomological sciences, pest management, and laboratory services. Various types of field services are provided upon request.

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

HSHB-MO-T (40)

1991

MEMORANDUM FOR Executive Director, Armed Forces Pest Management Board, Forest Glen Section, WRAMC, Washington, DC 20307-5001

SUBJECT: Phase 4, Toxicological Study No. 75-51-0497-91, Assessment of the Developmental Toxicity of Zinc Naphthenate in Rats, June 1985 - July 1988

Copies of subject report with Executive Summary are enclosed.

FOR THE COMMANDER:

MAURICE H. WEEKS
Chief, Toxicology Division

CF:
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17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
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19. ABSTRACT (Continue on reverse if necessary and identify by block number) This study was designed to detect any potential developmental toxicity and/or teratogenic hazard associated with the use of zinc naphthenate as a wood preservative. Oral administration of zinc naphthenate to rats during the major period of fetal organogenesis did not result in teratogenic effects. Transient maternal toxicity was confined to the highest dosage group (938 mg/kg/day) and consisted of lethargy and lower body weight gain. Maternal treatment at that dosage level also produced a higher incidence of resorptions and lower average fetal body weight. Dams receiving zinc naphthenate, 94 or 188 mg/kg/day, were not effected; nor were their developing fetuses. Under the conditions of this study, zinc naphthenate was found to effect the developing fetus only at a dosage level which produced toxic signs in the maternal animal. In order to minimize human exposure, appropriate personal protection should be employed when handling all formulated wood preservatives, including those containing zinc naphthenate.

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DEPARTMENT OF THE ARMY
U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

EXECUTIVE SUMMARY
PHASE 4
TOXICOLOGICAL STUDY NO. 75-51-0497-91
ASSESSMENT OF THE DEVELOPMENTAL TOXICITY OF ZINC NAPHTHENATE IN RATS
JUNE 1985 - JULY 1988

1. PURPOSE. The U.S. Army Materiel Command is considering alternatives to replace pentachlorophenol as a wood preservative for use on wooden packaging, pallets and skids. Increasing awareness of health hazards associated with the use of pentachlorophenol has prompted an investigation into other commercially available products. One of the alternative preservative treatments utilizes zinc naphthenate as the active ingredient. This study was conducted to determine the effects of oral administration of zinc naphthenate on fetal development in rats. Results of this study, along with those of other toxicity studies, will be used to establish potential human health hazards related to applying zinc naphthenate-based preservatives and handling treated end products.

2. ESSENTIAL FINDINGS. Oral administration of zinc naphthenate to rats during the major period of fetal organogenesis did not result in teratogenic effects. Transient maternal toxicity was confined to the highest dosage group (938 mg/kg/day) and consisted of lethargy and lower body weight gain. Maternal treatment at that dosage level also produced a higher incidence of resorptions and lower average fetal body weights. Dams receiving zinc naphthenate, 94 or 188 mg/kg/day, were not effected; nor were their developing fetuses.

3. CONCLUSIONS. Under the conditions of this study, zinc naphthenate was found to effect the developing fetus only at a dosage level which produced toxic signs in the maternal animal.

4. RECOMMENDATIONS. In order to minimize human exposure, appropriate personal protection should be employed when handling all formulated wood preservatives, including those containing zinc naphthenate. Individual components of wood preservative treatments should be evaluated for developmental toxicity potential.

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

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PHASE 4
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I. REFERENCES. See Appendix A for a listing of references.

II. AUTHORITY.

A. Letter, U.S. Army Armament, Munitions and Chemical Command, DRSMC-LCU-SP(D), 30 January 1984, subject: Toxicological Hazards of Pentachlorophenol, Copper Naphthenate, Copper-8-Quinolinolate and Zinc Naphthenate, with endorsement thereto.

B. Letter, Armed Forces Pest Management Board (AFPMB), Washington, DC, 25 September 1984, subject: Toxicology of Wood Preservatives.

III. PURPOSE. This study was designed to assess the potential for zinc naphthenate to adversely effect the development of fetal rats. Results will aid in identifying potential health hazards of this material when used as an active ingredient in dipped, sprayed or painted wood preservative treatments.

IV. BACKGROUND.

A. The U.S. Army Materiel Command (AMC) has taken action to eliminate reference to Federal Specification TT-W-572, Wood Preservative: Water Repellent, from those specifications over which that command has custody. The TT-W-572 characterizes generic types of pentachlorophenol, copper naphthenate and copper-8-quinolinolate. The deletion of that reference was prompted by the increasing awareness of health hazards associated with pentachlorophenol. In lieu of referencing TT-W-572, the USA Armament Research, Development and Engineering Center (ARDEC) inserted two commercially available water-based preservatives into each document pertaining to treated wooden ammunition packaging, pallets and skids. One of these preservatives was identified as M-Gard W-550 (zinc naphthenate, Mooney Chemicals, Inc.). Although the Office of The Surgeon General, upon review of the modified specifications, did not concur with the sole sourcing of commercial products, this item may, in fact, have been the only "water-emulsifiable" form of zinc naphthenate available (reference 1).

B. The U.S. Army Medical Bioengineering Research and Development Laboratory (USAMBRDL) has conducted both a literature search and several acute toxicity studies on alternative wood preservatives. The literature search showed that limited published data were available on the compounds to be studied by this Agency (reference 2). Acute animal toxicity studies on water-based zinc naphthenate revealed low to moderate toxicity via the oral, ocular and dermal routes (reference 3).

C. A search of available literature and the data bases of the National Library of Medicine confirmed the deficiency of existing toxicity information on zinc naphthenate. Further examination of the files of the U.S. Environmental Protection Agency (EPA) yielded a number of studies already performed by several producers and formulators on their registered formulated products. No studies were reported specifically for zinc naphthenate, the active ingredient. There was no reported evidence of a previously conducted developmental toxicity study in any species for that compound.

D. Acute studies for zinc naphthenate, performed at the U.S. Army Environmental Hygiene Agency (USAEHA), have been previously reported (reference 4). These studies included primary skin and eye irritation, acute oral and dermal toxicity, skin sensitization, saturated vapor inhalation, mutagenicity screening, dominant lethal, avian toxicity, aquatic toxicity and Shimkin mouse assay. The results of these studies indicated that zinc naphthenate has a relatively low degree of toxicity.

V. TEST MATERIAL. The test material was supplied by Mooney Chemicals, Inc., 2301 Scranton Road, Cleveland, OH 44113-9988. Zinc naphthenate, technical, CAS No. 12001-85-3, was specially prepared by Mooney Chemicals for these studies. The compound, although an active ingredient, is not normally produced as an end product. It was a dark brown, tarry compound having a charcoal odor. The sample number was P-17448 and contained 13.7 percent zinc. Solutions, made to facilitate dosing, were prepared with corn oil (Mazola) and used on the day of preparation. The concentrations of zinc naphthenate were 500 mg/mL for the pilot study and 250 mg/mL for the main study.

VI. ANIMALS.

A. Sexually mature virgin female and naive male Sprague-Dawley rats, 9 to 12 weeks of age were used to produce pregnancies. These rats were obtained from Charles River Breeding Laboratories and were identified as CRL:COBS-CD-(SD)BR colony animals.

B. All rats were maintained in a temperature-, humidity- and light-controlled room. The conditions were 70 F ± 5, 50 percent ± 5 percent and a 12-hour light/dark cycle. A certified pesticide-free rodent chow and water were available ad libitum (reference 5).

C. Animals were housed in hanging-type cages 20 cm wide, 20 cm high and 30 cm deep for the one-on-one mating procedure. Following mating, females were housed three per unit in hanging wire cages 40 cm wide, 16 cm high and 35 cm deep.

VII. METHODS. The object of these studies was to detect any disruption in the normal process of fetal development which could be attributed to oral maternal exposure to zinc naphthenate. This could best be accomplished by oral administration of the test material to the maternal animals from the time of embryonic implantation through the period during which the major organ systems are formed. It was also desirable to produce some sign of maternal toxicity in rats receiving the highest daily dosage of zinc naphthenate. If development was unaffected where maternal toxicity was observed, zinc naphthenate would not be regarded as a developmental toxicant in this test system. To achieve this endpoint, the laboratory studies were divided into two subsets. A pilot study was first performed to establish acceptable dosage levels for the main developmental toxicity (reference 6).

A. Pilot Study.

1. The mating procedure consisted of housing one male with one female rat. The occurrence of copulation was established by daily (morning) inspection for sperm plugs on the pad under the cage. A positive finding set day 0 of gestation. Thirty-six positively mated female rats were identified by toe clip, housed individually, and assigned among five treatment and one control dosage group. Dosages of zinc naphthenate selected as fractions of the previously determined oral ALD, (7500 mg/kg) were 1875, 938, 469, 235 and 118 mg/kg/day. Single daily doses of the compound, in a 250 mg/mL corn oil solution, were administered by gavage beginning on day 6 of gestation and continued up to and including day 15 of gestation. The control group received the vehicle only, (7.50 mL/kg) on a comparable regimen. Individual daily doses were based on the maternal animal's body weight on day 6 of gestation.

2. All females were observed daily for changes in appearance and behavior. A gross necropsy was performed on all rats which died before the scheduled sacrifice day.

3. All females were weighed on gestation days 0, 6, 10, 13, 16 and 20.

4. On the morning of the twentieth day of gestation, each female (dam) was sacrificed by carbon dioxide (CO_2) inhalation and the uterus and ovaries exposed by laparotomy. The number and location of viable fetuses, nonviable fetuses, resorptions, total implantations, and corpora lutea were recorded. The dams were examined for gross pathological changes before being discarded. Fetuses were individually weighed, measured, sexed, and examined for external malformations. Each fetus was then dissected and examined for external anomalies before being discarded. These fetal examinations were conducted to screen for potential fetal toxicity and/or teratogenicity.

5. The lowest dosage level significantly affecting group maternal weight gain or producing other outward signs of group maternal toxicity was chosen as the highest dosage level for the teratology study.

B. Main Developmental Toxicity Study.

1. Upon completion of the pilot study, 150 female and 52 male rats began a mating program. The mating procedure continued until there were at least 33 positively mated females in each dose group.

2. Daily oral dosing commenced on day 6 of gestation and continued through day 15 of gestation. Daily dosages of zinc naphthenate selected for this study were 94, 188 and 938 mg/kg/day. Zinc naphthenate was mixed with corn oil to make a 250 mg/mL solution. Vehicle controls received 3.75 mL/kg/day of corn oil.

3. All females were observed daily for clinical and behavioral deviations from normal. Animals were weighed on days 0, 6, 10, 13, 16 and 20 of gestation. Any rats found dead or moribund during the course of the study were submitted for gross necropsy.

4. On day 20 of gestation, females (dams) were sacrificed by CO_2 inhalation. Each uterus was exposed and counts were made of corpora lutea, implantation sites, resorptions, and fetuses. The gravid uterus was then excised and weighed. This weight was subtracted from the terminal female body weight in order to determine absolute body weight gain/loss during gestation. All fetuses were removed from the uterus and assigned a number, starting from the dam's upper right horn and proceeding to the dam's upper left horn. After measurement of weight, as

well as gross observation and sexing, all fetuses were tagged for permanent identity. Odd-numbered fetuses were placed in denatured ethanol for skeletal preparation while even-numbered fetuses were placed in Bouin's fixative for soft tissue examination. A record of the above sacrifice procedures were recorded on HSE-LT Form 40, Prenatal Toxicity Record.

5. Fetal examinations were conducted per reference 6. Findings were recorded on either HSE-LT Form 53-1, Fetal Skeletal Examination or HSE-LT Form 53, Soft Tissue Examination.

6. Experimental data were collected on the specialized forms, large tabular sheets, or in laboratory notebook number 104. Statistical analyses were performed on maternal, litter, and fetal data. Only those differences between treated and control group values which were significant at $P < 0.05$ were reported. Analyses of fetal data were performed based on the litter as the experimental unit.

a. Group data. The following group parameters were calculated or counted without statistical analysis using the accompanying definitions (reference 7):

(1) Parameters.

(a) Fertility index = $\frac{\text{pregnant animals}}{\text{positively mated animals at terminal sacrifice}} \times 100$

(b) Gestation index = $\frac{\text{viable litters}}{\text{pregnant animals}} \times 100$

(c) Index of alive fetuses = $\frac{\text{alive fetuses}}{\text{total fetuses}} \times 100$

(d) Resorption index = $\frac{\text{total number of resorptions}}{\text{total number of implantations}} \times 100$

(e) Malformation index =

$$\frac{\text{total number of fetuses with malformations}}{\text{total number of fetuses}} \times 100$$

(f) Variation index =

$$\frac{\text{total number of fetuses with variations}}{\text{total number of fetuses}} \times 100$$

(g) Number of runts.

(2) Definitions.

(a) Early Resorption. Reabsorption of the conceptus by the dam in the early stages of pregnancy. Deciduoma or placental remains without embryonic remains are the criteria for this observation.

(b) Late Resorption. Reabsorption of the conceptus by the dam in the late stages of pregnancy. Placental and fetal remains are the criteria for this observation.

(c) Malformation. A morphologic defect of an organ, part of an organ or larger region of the body resulting from an intrinsically abnormal developmental process. A malformation is not naturally reversible.

(d) Variation. A minor morphologic deviation known to occur within the species and of no consequence to the reasonable development of the animal.

(e) Normal. No malformations or variations.

(f) Runt. A fetus weighing 70 percent or less than the mean weight of its litter.

b. Maternal Data. Maternal body weight and body weight gain were analyzed using a one-way analysis of variance followed by Dunnett's test.

c. Litter Data.

(1) Number Per Litter. The number of corpora lutea, implantations and live fetuses per litter were analyzed using the t-test.

(2) Percent Per Litter. Percentage data, which included percent female (sex ratio), resorptions, malformations, *variations and normal fetuses per litter, were transformed* by the angular transformation and analyzed using a t-test.

(3) Percent of Litters With An Effect. The percent of litters which contained a runt, resorption, dead fetus, malformation or variation was analyzed using chi-square and the square root of chi-square. The percent of litters which contained all normal fetuses was analyzed in the same manner.

d. Fetal Data. Fetal body weights were analyzed by a nested one-way analysis of variance.

7. The USAEHA Quality Assurance Office approved the study plan and associated Standing Operating Procedures (SOPs). Each phase of this study was inspected by that Office to ensure that the study plan and SOPs were adhered to. A certification appears as Appendix B.

VIII. RESULTS.

A. Pilot Study.

1. All females receiving zinc naphthenate, 1875 mg/kg/day, were pregnant. Only one of these dams lived for the duration of the study. However, none of her conceptuses were viable. Observable maternal toxic signs at this dosage level consisted of lethargy, brown/urine-stained urogenital areas, red nasal discharge, and generalized alopecia.

2. All pregnant females receiving zinc naphthenate, 938 mg/kg/day, lived for the duration of the study. Pups derived from these dams were externally normal and were not statistically different from the control pups in either weight or length. Observable maternal toxic signs at this dosage level consisted of moderate amounts of generalized alopecia.

3. All pregnant females receiving zinc naphthenate, 469 mg/kg/day, 235 mg/kg/day and 118 mg/kg/day lived for the duration of the study. Maternal rats at these dosage levels were asymptomatic. Their pups were externally normal.

B. Main Developmental Toxicity Study.

1. Group Parameters. Group indices, averages, and other summary data are presented in Table 1.

a. Dams receiving 938 mg/kg/day of zinc naphthenate had a significantly greater number of implantation sites on the average than control and lower dosage groups. Dams in that group also had a significantly higher average number of resorptions. Differences in those two parameters netted a result of no overall difference in fetuses per dam.

b. Fetal variations were significantly more prevalent in groups receiving zinc naphthenate, 188 and 94 mg/kg/day.

c. There were no other differences in group parameters among control and treatment sets.

TABLE 1. GROUP PARAMETERS

	Zinc Naphthenate Oral Developmental Study in Rats			
	Control	94 mg/kg	188 mg/kg	938 mg/kg
Females mated	33	33	33	33
Fatalities	0	0	1	1
Females at sacrifice	33	33	32	32
Females pregnant	33	31	32	32
Fertility Index (%)	100	94	100	100
Litters	33	31	32	31
Gestation Index (%)	100	100	100	97
Implantations, total	480	459	473	505
Implantations per dam	14.5	14.8	14.8	15.8*
Fetuses, total	451	439	434	431
Fetuses per dam	13.7	14.2	13.5	13.4
Dead fetuses, total	0	0	1	0
Dead fetuses per dam	0	0	.03	0
Index of Alive Fetuses (%)	100	100	99	100
Resorptions, total	29	20	38	74*
Early resorptions	27	20	38	72*
Late resorptions	2	0	0	2
Resorptions per dam	0.9	0.6	1.2	2.31*
Resorption Index (%)	6.0	4.4	8.0	14.7*
Malformations, total	0	0	1	2
Fetuses w/ malformations	0	0	1	1
Litters with malformations	0	0	1	1
Malformations per dam	0	0	0.03	0.03
Malformation index (%)	0	0	0.2	0.2
Variations, total	11	23*	33*	24*
Fetuses w/ variations	10	23*	33*	22*
Litters with variations	7	14*	18*	14*
Variations per dam	.30	.74*	1.03*	.69*
Variation index (%)	2.2	5.2*	7.6*	5.1*
Runts	1	1	2	2
Sex ratio (M/F)	0.98	1.12	1.05	1.04

* Significantly different from Controls at the 0.05 level of probability

2. Maternal Parameters.

a. One pregnant female from each of the groups receiving zinc naphthenate at levels of 188 mg/kg/day and 938 mg/kg/day died from dosing errors.

b. Premortem signs for dams receiving zinc naphthenate at 938 mg/kg/day included brown-stained urogenital areas, red nasal and oral exudate, generalized alopecia, and lethargy.

c. Control dams and dams receiving zinc naphthenate at 188 mg/kg/day or 94 mg/kg/day were asymptomatic during the course of the study.

d. Maternal body weights and body weight gains for zinc naphthenate-treated rats, 938 mg/kg/day, were significantly lower on gestation day 10 then for any of the other dosage groups. However, by gestation day 13 up until the time of necropsy on day 20, there was no significant difference between maternal body weights or body weight gain among any of the dosage groups. A summary of maternal body weights is presented in Table 2. Maternal body weight gains are summarized in Table 3. Individual maternal body weights are given in Appendix C.

TABLE 2. MEAN MATERNAL BODY WEIGHTS (grams)

Exposure Group	Zinc Naphthenate Oral Developmental Study in Rats						
	Gestation Day						20
	0	6	10	13	16	20	Adjusted
Control	240 ±14	262 ±16	277 ±19	293 ±19	313 ±22	363 ±23	290 ±20
94 mg/kg/day	237 ±11	259 ±14	273 ±16	288 ±17	305 ±20	365 ±29	286 ±18
188 mg/kg/day	240 ±16	264 ±18	276 ±19	291 ±18	308 ±21	364 ±26	287 ±21
938 mg/kg/day	241 ±16	265 ±20	263* ±25	281 ±25	297 ±27	356 ±34	285 ±24

* Significantly lower than Controls at the 0.05 level of probability.

TABLE 3. MEAN MATERNAL BODY WEIGHT GAIN (grams)

Exposure Group	Zinc Naphthenate Oral Developmental Study in Rats Gestation Day 6	10	13	16	20	20 Adjusted
Control	22 ± 7	15 ± 6	16 ± 4	20 ± 7	50 ±19	-73 ±20
94 mg/kg/day	23 ± 7	14 ± 7	15 ± 5	17 ± 8	60* ±14	-79 ±16
188 mg/kg/day	23 ± 9	12 ± 6	15 ± 4	17 ± 9	56 ±11	-77 ±15
938 mg/kg/day	24 ± 8	-2* ±13	18 ± 7	17 ± 8	58 ±14	-71 ±17

* Significantly different from controls at the 0.05 level of probability.

3. Litter and Fetal Parameters. These elements are summarized in Tables 4 and 5. Individual litter data are presented in Appendix D.

a. Fetuses from dams receiving zinc naphthenate at 938 mg/kg/day had significantly lower body weights, on the average, than control fetuses or fetuses of the lower dosage groups. Variances between fetal parameters of control and zinc naphthenate, 188 mg/kg/day and 94 mg/kg/day, were not significant.

b. No dose relationship was established for fetal variations, although as stated for group parameters, fetuses from dams receiving zinc naphthenate, 188 mg/kg/day, had a significantly higher incidence of variants than corn oil controls. Fetuses from dams receiving 938 mg/kg/day of zinc naphthenate showed a slightly higher incidence of variation than controls. There was no trend toward delayed ossification among fetuses from 938 mg/kg/day litters.

c. There was a notable increase in the percentage of litters with resorptions among dams receiving 938 mg/kg/day of zinc naphthenate.

d. Other litter and fetal parameters were unaffected by maternal exposure to zinc naphthenate.

TABLE 4. LITTER AND FETAL PARAMETERS

	Zinc Naphthenate Oral Developmental Study in Rats			
	Control	94 mg/kg	188 mg/kg	938 mg/kg
Corpora lutea/litter	16.2	16.0	15.9	16.4
Implantation sites/ litter	14.5	14.8	14.8	15.8*
Live fetuses/litter	13.7	14.2	13.5	13.4
% of conceptuses resorbed/litter	6.2	4.1	8.1	14.6*
% of litters with resorption	52	52	59	75*
Dead fetuses/litter	0	0	0.03	0
Average fetal body weight	3.41	3.45	3.43	3.09*
% of litters with runts	3	3	6	6
% female/litter	51	47	49	49
% of fetuses/litter w/malformation	0	0	0.2	0.2
% of fetuses/litter w/variation	2.2	5.2*	7.6*	5.1*
% of normal fetuses/ litter	97.8	94.8	92.4	94.9
% of litters w/ malformation	0	0	3.1	3.1
% of litters w/ variation	21.2	45.2*	68.8*	43.8*
% of litters w/ all normal fetuses	78.8	54.8*	28.1*	53.1*

* Significantly different than Controls at the 0.05 level of probability.

TABLE 5. SUMMARY OF MALFORMATIONS AND VARIATIONS

	Zinc Naphthenate Oral Developmental Study in Rats			
	Control	94 mg/kg	188 mg/kg	938 mg/kg
Number of fetuses examined (Number of litters)	451 (33)	439 (31)	434 (32)	431 (31)
Malformations				
Exencephaly	0 (0)	0 (0)	0 (0)	1 (1)
Exopthalmia	0 (0)	0 (0)	0 (0)	1 (1)
Constriction ring (tail)	0 (0)	0 (0)	1 (1)	0 (0)
Variations				
Reduced ossification				
Hyoid	3 (3)	1 (1)	1 (1)	5 (4)
Skull	4 (3)	11 (7)	12 (7)	8 (7)
Pelvis	0 (0)	0 (0)	0 (0)	1 (1)
Sternebra(e), misaligned	0 (0)	0 (0)	0 (0)	3 (2)
Sternebra(e), bifid	1 (1)	0 (0)	0 (0)	0 (0)
Extra thoracic rib(s)	0 (0)	0 (0)	1 (1)	2 (2)
Ecchymosis	1 (1)	1 (1)	2 (2)	3 (3)
Orbit, hemorrhagic	0 (0)	0 (0)	1 (1)	0 (0)
Brain, enlarged lateral ventricle	0 (0)	5 (1)	0 (0)	0 (0)
Renal papillae, not well developed	0 (0)	1 (1)	12 (6)	0 (0)
Testicle, not well developed	0 (0)	0 (0)	1 (1)	0 (0)
Testicle, not fully descended	2 (1)	4 (3)	3 (3)	2 (2)

IX. DISCUSSION AND CONCLUSIONS.

A. With the potential increased usage of zinc naphthenate as a wood preservative treatment, exposure to that material may become widespread among military and civilian populations. Acute studies in rats and rabbits previously reported indicate that zinc naphthenate is characterized by a relatively low degree of toxicity by the oral and dermal routes of administration (reference 4). Although human exposure would most likely be expected dermally, oral administration was chosen for this study

to increase the degree of absorption of zinc naphthenate and to avoid skin irritation which would have been associated with repeated application. The oral dosage levels selected for this developmental study reflect the low degree of toxicity and are well above any realistic routine human exposure by either the oral or dermal routes.

B. Maternal toxicity was limited to rats receiving 938 mg/kg/day. Toxicity was manifest as significantly lower body weights following the onset of exposure with a trend toward normalization of weight gain after the initial depression. Other signs of toxicity such as lethargy and nasal discharge were transient. This pattern of symptoms suggests that 938 mg/kg/day, the highest dosage administered, very closely represents the lowest observed adverse effect level (LOAEL) for zinc naphthenate in the maternal rats.

C. Average fetal body weights were significantly lower at 938 mg/kg/day when compared to controls and other zinc naphthenate dosage groups. This effect, along with a significant increase in resorptions per dam at that dosage, is a demonstration that the test compound may be a developmental toxicant in rats at a dosage level which produces signs of maternal toxicity. The evidence is inconclusive in that a significant increase in the number of implantation sites per dam at 938 mg/kg/day may have adversely influenced resorptions and fetal body weight.

D. There was no tendency toward a dose-related increase in malformed or variant fetuses. It is notable that at a maternal dosage which depressed fetal body weight, there was no corresponding retardation of skeletal development. Studies reported for Ampicillin, o-Chloro-p-phenylenediamine and Dibromochloropropane indicate that this finding is not unique to zinc naphthenate (reference 8). It is concluded that zinc naphthenate is not teratogenic in rats at the dosage levels tested.

E. Zinc naphthenate is the active ingredient in certain wood preservative formulations. Other components in such formulations include mineral spirits and emulsifiers. A search of the data bases of the National Library of Medicine yielded no information concerning the developmental toxicity potential of the additional materials in the formulation. Although not reported as teratogenic, these components present unknown factors in the overall developmental toxicity of preservative treatments.

X. RECOMMENDATIONS. The following recommendations are based on the professional scientific judgement of the investigators.

A. Protective eyewear, gloves and coveralls should be worn by individuals in areas where zinc naphthenate preservative treatments are being applied.

B. Studies indicate that zinc naphthenate-treated wood should not be considered a developmental toxicity hazard.

C. Individual components of wood preservative treatments should be evaluated for developmental toxicity potential.

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APPENDIX A

REFERENCES

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2. Preliminary Report, U.S. Army Medical Bioengineering Research and Development Laboratory, undated, subject: A Preliminary Toxicological Evaluation of Eight Chemicals Used as Wood Preservatives.

3. Muni, I.A., Gordon, E.B., and Goodband, J.B., Dermal, Eye and Oral Toxicological Evaluations, Wood Preservatives, Phase 1 Report, December 1983.

4. Letter, USAEHA, HSHB-MO-T, 21 April 1987, subject: Phase 1, Preliminary Assessment of the Relative Toxicity of Zinc Naphthenate, Study No. 75-51-0497-87, May 1984-June 1986.

5. Toxicology Division, Standing Operating Procedure No. 4, Animal Facilities Buildings E-2100 and E-2101, March 1982.

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7. A.K. Palmer, Handbook of Teratology, Vol IV, Chapter 8, "The Design of Subprimate Animal Studies," pp. 215-253, Plenum Press, New York, New York, 1978.

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9. Memorandum, USAEHA, HSHB-MO-T, 5 January 1988, subject: Phase 2, Preliminary Assessment of the Relative Toxicity of Copper Naphthenate, Acute Studies, Study No. 75-51-0497-88, May 1984 - June 1986.

10. Memorandum, USAEHA, HSHB-MO-T, 16 November 1988, subject: Phase 3, Preliminary Assessment of the Relative Toxicity of Copper Naphthenate (Mooney Chemicals), Acute Studies, Study No. 75-51-0497-88, May 1984 - October 1987.

APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

1. This study was conducted in accordance with:

a. Standing Operating Procedures developed by the Toxicology Division, USAEHA.

b. Title 21, Code of Federal Regulations (CFR), 1990 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

2. Facilities were inspected during the operational phases of this study to ensure compliance with paragraph a, above. A summary of inspection dates and findings in the Annex.

3. The information presented in this report accurately reflects the raw data generated during the course of conducting this study.

TIMOTHY L. FISHER
Chief, Analytical Quality
Assurance Division

ANNEX

QUALITY ASSURANCE INSPECTION DATES, REPORTS AND FINDINGS

1. Phase 4 of Toxicological Study No. 75-51-0497-91 was inspected by a representative of the Analytical Quality Assurance Office on the following dates:

2, 10, 14 and 15 May 1985
4, 6, 7, 11, 12, 18, 25 and 26 June 1985
17 July 1985
9 September 1985
21 October 1985

2. Quality Assurance Review Reports were reported to management on the following dates:

15 May 1985
31 May 1985
4 June 1985
9 July 1985
14 November 1985

3. There were not findings which would have affected the integrity of the study herein reported.

APPENDIX C

INDIVIDUAL BODY WEIGHTS

APPENDIX C
INDIVIDUAL BODY WEIGHTS (grams)
CONTROL

DAM ID	DAY 0	DAY 6	DAY 10	DAY 13	DAY 16	DAY 20	DAY 20 ADJUSTED
239	215	240	256	273	296	355	269
243	234	247	247	272	290	347	261
247	208	236	244	259	284	336	260
251	238	262	276	288	316	369	303
255	244	269	288	303	324	381	296
259	245	272	283	304	324	372	303
263	242	260	265	284	300	372	281
267	236	248	268	286	305	358	284
271	233	250	265	283	305	371	280
275	259	289	305	324	329	392	307
279	219	252	266	283	297	324	291
283	238	262	284	297	322	374	288
287	235	272	288	307	324	370	288
291	231	263	271	286	292	313	294
295	246	263	289	309	337	389	307
299	246	260	282	293	312	370	296
303	223	241	262	277	293	347	261
307	226	241	255	270	289	343	257
311	248	278	291	309	326	385	303
315	242	263	278	298	314	357	307
319	238	254	265	278	291	334	269
323	257	282	300	314	336	393	313
327	231	248	259	272	297	359	270
331	218	241	261	275	296	348	275
335	248	271	280	300	321	383	282
339	234	252	258	269	284	319	270
343	239	254	266	284	297	353	286
347	254	268	281	285	307	360	289
351	257	272	287	300	319	383	294
355	246	269	283	295	321	363	293
359	257	283	305	317	348	410	324
363	265	307	333	352	391	353	343
367	262	282	296	311	334	389	311

APPENDIX C
INDIVIDUAL BODY WEIGHTS (grams)
94 MG/KG ZINC NAPHTHENATE

DAM ID	DAY 0	DAY 6	DAY 10	DAY 13	DAY 16	DAY 20	DAY 20 ADJUSTED
240	231	252	260	278	293	329	285
244	218	235	246	264	275	330	260
248	223	246	260	278	293	347	273
252	248	278	297	315	343	417	329
256	249	282	295	313	337	408	307
260	255	281	271	295	319	393	293
264	265	a	a	a	a	a	a
268	226	244	254	269	293	357	264
272	211	233	245	258	273	315	257
276	220	247	264	278	295	366	275
280	242	272	286	306	333	403	310
284	229	238	244	256	264	289	262
288	238	262	283	293	311	366	288
292	243	274	292	306	333	390	301
296	225	245	264	276	296	348	266
300	235	260	272	285	299	364	281
304	253	281	302	320	336	400	307
308	232	251	275	292	311	369	284
312	242	274	292	308	330	390	310
316	230	252	273	283	300	365	278
320	243	259	266	282	299	346	279
324	239	259	273	282	289	348	265
328	245	265	279	295	311	367	289
332	238	261	271	286	304	356	280
336	230	240	250	270	287	338	271
340	236	267	288	302	296	390	299
344	245	277	296	318	319	402	314
348	238	255	277	270	294	363	278
352	239	265	281	296	313	388	296
356	243	a	a	a	a	a	a
360	237	265	271	284	306	354	293
364	232	262	273	287	313	374	289
368	230	244	256	270	291	338	271

a - Animal Found Dead

APPENDIX C
INDIVIDUAL BODY WEIGHTS (grams)
188 MG/KG ZINC NAPHTHENATE

DAM ID	DAY 0	DAY 6	DAY 10	DAY 13	DAY 16	DAY 20	DAY 20 ADJUSTED
241	239	260	268	282	299	361	276
245	228	254	267	283	305	364	282
249	233	270	279	297	313	369	271
253	203	222	235	254	271	329	246
257	245	284	288	304	324	373	315
261	228	249	260	283	298	344	287
265	236	252	262	275	288	328	263
269	243	273	287	306	311	352	284
273	216	a	a	a	a	a	a
277	236	249	261	279	300	351	283
281	221	244	253	269	281	338	260
285	251	278	289	303	323	391	305
289	219	252	276	282	296	355	273
293	245	293	283	303	325	365	310
297	266	279	297	299	327	362	306
301	244	263	279	297	293	370	292
305	259	269	288	303	332	393	288
309	238	253	272	285	302	350	284
313	254	278	295	313	335	408	319
317	249	276	286	301	321	382	301
321	226	252	264	283	295	351	284
325	234	247	251	267	285	351	267
329	243	255	271	286	300	336	283
333	229	253	262	279	298	373	278
337	246	261	268	277	295	341	263
341	227	243	252	269	282	333	264
345	248	275	278	290	311	368	287
349	252	285	299	317	341	418	318
353	237	249	261	277	306	366	264
357	237	259	275	284	268	318	271
361	287	308	326	342	351	414	338
365	251	289	305	317	335	396	315
369	262	280	298	306	340	395	308

a - Animal Found Dead

APPENDIX C
INDIVIDUAL BODY WEIGHTS (grams)
938 MG/KG ZINC NAPHTHENATE

DAM ID	DAY 0	DAY 6	DAY 10	DAY 13	DAY 16	DAY 20	DAY 20 ADJUSTED
242	223	244	254	275	294	340	275
246	225	248	259	275	289	340	265
250	237	274	273	294	301	388	308
254	250	268	277	278	298	366	302
258	231	254	246	263	267	326	262
262	229	250	236	240	261	324	267
266	234	250	248	272	295	366	279
270	227	235	226	240	253	314	246
274	208	233	245	266	279	340	254
278	231	255	228	253	260	309	277
282	233	254	251	266	270	335	264
286	227	263	277	287	303	364	283
290	240	267	229	250	265	264	254
294	227	a	a	a	a	a	a
298	253	280	297	307	324	374	294
302	227	254	254	268	297	363	275
306	249	270	277	303	323	386	318
310	260	270	261	277	293	352	281
314	230	248	237	262	268	321	262
318	257	276	279	305	322	396	304
322	248	276	276	292	307	366	296
326	226	241	233	260	284	346	264
330	229	247	230	246	263	317	256
334	242	261	246	275	293	349	272
338	248	284	285	297	321	383	303
342	267	298	300	308	316	362	306
346	268	292	283	300	329	406	311
350	264	306	301	322	339	400	318
354	252	271	263	292	293	347	277
358	281	320	323	349	371	429	353
362	238	268	254	267	295	354	284
366	250	270	298	314	337	382	307
370	241	256	260	275	303	358	295

a - Animal Found Dead

APPENDIX D

INDIVIDUAL LITTER AND FETAL PARAMETERS

APPENDIX D
INDIVIDUAL LITTER AND FETAL PARAMETERS
CONTROL

DAM No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Sex M/F
239	20	18	1	0	1	17	0	17	3.25	8/9
243	18	15	0	0	0	15	0	15	3.81	3/12
247	16	15	1	1	2	13	0	13	3.51	8/5
251	18	12	1	0	1	11	0	11	3.68	5/6
255	18	16	1	0	1	15	0	15	3.81	8/7
259	18	12	0	0	0	12	0	12	3.47	7/5
263	15	14	0	0	0	14	0	14	3.2	6/8
267	19	14	0	0	0	14	0	14	3.19	7/7
271	18	17	0	0	0	17	0	17	3.31	10/7
275	22	18	1	1	2	16	0	16	3.45	10/6
279	13	9	4	0	4	5	0	5	3.45	2/3
283	16	17	1	0	1	16	0	16	3.47	10/6
287	16	16	2	0	2	14	0	14	3.72	9/5
291	8	3	1	0	1	2	0	2	4.3	1/1
295	15	15	1	0	1	14	0	14	3.7	9/5
299	18	16	1	0	1	15	0	15	2.92	8/7
303	17	15	0	0	0	15	0	15	3.65	8/7
307	15	16	0	0	0	16	0	16	3.39	10/6
311	16	19	3	0	3	16	0	16	2.93	9/7
315	14	9	0	0	0	9	0	9	3.16	4/5
319	11	12	0	0	0	12	0	12	3.24	7/5
323	16	14	1	0	1	13	0	13	3.9	2/11
327	20	17	0	0	0	17	0	17	3.24	14/3
331	14	13	0	0	0	13	0	13	3.45	6/7
335	20	19	0	0	0	19	0	19	3.24	7/12
339	13	8	0	0	0	8	0	8	3.54	5/3
343	13	13	2	0	2	11	0	11	3.43	1/10
347	12	15	2	0	2	13	0	13	3.43	4/9
351	16	15	0	0	0	15	0	15	3.73	9/6
355	12	12	0	0	0	12	0	12	3.56	2/10
359	17	17	2	0	2	15	0	15	3.61	9/6
363	24	24	2	0	2	22	0	22	3.88	8/14
367	17	15	0	0	0	15	0	15	2.98	7/8

APPENDIX D
INDIVIDUAL LITTER AND FETAL PARAMETERS
94 MG/KG ZINC NAPHTHENATE

DAM No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Sex M/F
240	12	8	1	0	1	7	0	7	3.67	4/3
244	12	14	1	0	1	13	0	13	3.09	7/6
248	13	14	1	0	1	13	0	13	3.75	8/5
252	21	15	0	0	0	15	0	15	3.53	7/8
256	18	19	1	0	1	18	0	18	3.46	12/6
260	16	17	0	0	0	17	0	17	3.57	6/11
268	16	17	0	0	0	17	0	17	3.43	9/8
272	14	12	2	0	2	10	0	10	3.5	5/5
276	21	18	1	0	1	17	0	17	3.29	10/7
280	18	18	1	0	1	17	0	17	3.37	8/9
284	11	5	1	0	1	4	0	4	4.02	1/3
288	16	15	2	0	2	13	0	13	3.79	7/6
292	18	17	0	0	0	17	0	17	3.21	8/9
296	17	15	0	0	0	15	0	15	3.28	10/5
300	18	16	1	0	1	15	0	15	3.4	8/7
304	17	16	1	0	1	15	0	15	3.73	6/9
308	15	16	0	0	0	16	0	16	3.35	10/6
312	14	16	1	0	1	15	0	15	3.27	6/9
316	18	16	0	0	0	16	0	16	3.33	4/12
320	17	15	3	0	3	12	0	12	3.18	6/6
324	17	17	1	0	1	16	0	16	3.3	11/5
328	19	14	0	0	0	14	0	14	3.38	7/7
332	13	14	0	0	0	14	0	14	3.53	7/7
336	13	13	1	0	1	12	0	12	3.39	6/6
340	15	17	0	0	0	17	0	17	3.04	7/10
344	16	16	0	0	0	16	0	16	3.19	7/9
348	15	14	0	0	0	14	0	14	3.79	9/5
352	21	16	0	0	0	16	0	16	3.68	13/3
360	12	11	0	0	0	11	0	11	3.22	6/5
364	19	15	0	0	0	15	0	15	3.6	10/5
368	13	13	1	0	1	12	0	12	3.47	7/5

APPENDIX D
INDIVIDUAL LITTER AND FETAL PARAMETERS
188 MG/KG ZINC NAPHTHENATE

DAM No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Sex M/F
241	17	16	1	0	1	15	0	15	3.49	7/8
245	17	15	0	0	0	15	0	15	3.39	7/8
249	19	15	0	0	0	15	0	15	3.45	5/10
253	18	17	1	0	1	16	0	16	3.4	8/8
257	13	16	6	0	6	10	0	10	3.27	3/7
261	13	10	0	0	0	9	1	10	3.25	4/6
265	13	14	2	0	2	12	0	12	3.42	9/3
269	16	14	1	0	1	13	0	13	3.15	6/7
277	16	14	1	0	1	13	0	13	3.25	7/6
281	13	15	1	0	1	14	0	14	3.39	5/9
285	18	16	1	0	1	15	0	15	3.49	10/5
289	16	14	0	0	0	14	0	14	3.68	8/6
293	14	9	0	0	0	9	0	9	3.55	5/4
297	16	9	0	0	0	9	0	9	3.51	4/5
301	18	16	0	0	0	16	0	16	3.08	6/10
305	15	17	3	0	3	14	0	14	5.28	8/6
309	13	13	1	0	1	12	0	12	3.26	3/9
313	22	16	0	0	0	16	0	16	3.35	7/9
317	16	15	0	0	0	15	0	15	3.34	5/10
321	13	12	1	0	1	11	0	11	3.4	6/6
325	20	17	3	0	3	14	0	14	3.72	10/4
329	14	15	6	0	6	9	0	9	3.5	8/1
333	18	17	0	0	0	17	0	17	3.57	11/6
337	16	16	2	0	2	14	0	14	3.37	7/7
341	14	13	1	0	1	12	0	12	3.58	5/7
345	17	16	0	0	0	16	0	16	3.02	8/8
349	14	18	1	0	1	17	0	17	3.75	11/6
353	18	16	0	0	0	16	0	16	4.71	11/5
357	12	14	2	0	2	12	0	12	1.92	5/7
361	15	15	1	0	1	14	0	14	3.48	6/8
365	17	17	3	0	3	14	0	14	3.4	9/5
369	17	16	0	0	0	16	0	16	3.25	9/7

APPENDIX D
INDIVIDUAL LITTER AND FETAL PARAMETERS
938 MG/KG ZINC NAPHTHENATE

DAM No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Sex M/F
242	17	16	3	0	3	13	0	13	2.83	6/7
246	18	17	2	0	2	15	0	15	3.14	5/10
250	18	17	2	0	2	15	0	15	3.22	7/8
254	15	16	3	0	3	13	0	13	2.91	7/6
258	14	15	3	0	3	12	0	12	3.09	8/4
262	18	14	2	0	2	12	0	12	2.58	7/5
266	16	17	1	0	1	16	0	16	3.28	5/11
270	13	15	2	0	2	13	0	13	3.02	7/6
274	13	17	0	0	0	17	0	17	3.04	6/11
278	17	13	6	1	7	6	0	6	2.34	1/5
282	18	15	2	0	2	13	0	13	3.49	9/4
286	15	15	0	0	0	15	0	15	3.38	5/10
290	16	16	16	0	16	0	0	0	0	0
298	15	15	0	0	0	15	0	15	3.01	6/9
302	19	17	2	1	3	14	0	14	4.41	9/5
306	18	14	2	0	2	12	0	12	3.18	6/6
310	15	16	3	0	3	13	0	13	3.07	5/8
314	12	14	2	0	2	12	0	12	2.75	7/5
318	19	16	0	0	0	16	0	16	3.32	9/7
322	15	15	1	0	1	14	0	14	2.95	9/5
326	17	18	0	0	0	18	0	18	2.78	10/8
330	13	15	3	0	3	12	0	12	3.04	6/6
334	14	16	1	0	1	15	0	15	2.94	10/5
338	18	15	0	0	0	15	0	15	3.15	10/5
342	19	19	9	0	9	10	0	10	2.9	5/5
346	21	19	1	0	1	18	0	18	3.24	9/9
350	20	16	1	0	1	15	0	15	3.26	8/7
354	15	15	0	0	0	15	0	15	2.62	10/5
358	20	17	0	0	0	17	0	17	2.75	6/11
362	13	13	1	0	1	12	0	12	3.22	5/7
366	17	17	2	0	2	15	0	15	3.13	10/5
370	17	15	2	0	2	13	0	13	2.79	7/6